In the Specification:

Please replace the following paragraphs in their entirety:

At Page 11:

[0017] In preferred embodiments, the synthetic mammalian expression plasmid comprises a pUC-18 prokaryotic origin of replication sequence. However, the origin of replication may also comprise an autonomously replication sequence ("ARS"). In a preferred embodiment, the optimized prokaryotic antibiotic resistant gene comprises kanamycin. In another preferred embodiment, the poly adenylation signal ("PolyA") comprises a human growth hormone ("hGH") poly A signal, and a hGH 5' untranslated region ("5'UTR"). The codon optimized mammalian therapeutic gene sequence comprises a sequence that encodes a modified species specific growth hormone releasing hormone ("GHRH"). In preferred embodiments, the codon optimized sequence comprises porcine, mouse, rat, bovine, ovine, and chicken GHRH (e.g. ~~SeqID#4~~ SEQ ID NO: 4, ~~SeqID#5~~ SEQ ID NO: 5; ~~SeqID#6~~ SEQ ID NO: 6; ~~SeqID#7~~ SEQ ID NO: 7; ~~SeqID#8~~ SEQ ID NO: 8; and ~~SeqID#9~~ SEQ ID NO: 9). Similarly, species specific, and codon optimized plasmids are disclosed (e.g. ~~SEQID#17~~ SEQ ID NO: 17; ~~SEQID#18~~ SEQ ID NO: 18; ~~SEQID#19~~ SEQ ID NO: 19; ~~SEQID#20~~ SEQ ID NO: 20; and ~~SEQID#21~~ SEQ ID NO: 21).

[0018] Another aspect of the current invention is a method for plasmid mediated gene supplementation that comprises delivering a codon optimized synthetic mammalian expression plasmid into a subject. The codon optimized synthetic mammalian expression plasmid encodes a growth hormone releasing hormone ("GHRH") or functional biological equivalent in the subject. The method of delivering the codon optimized synthetic mammalian expression plasmid into the cells of the subject is via electroporation. In a preferred embodiment, the cells of the subject can be somatic cells, stem cells, or germ cells. The codon optimized synthetic mammalian expression plasmids consisting of ~~SeqID#17~~ SEQ ID NO: 17, ~~SeqID#18~~ SEQ ID NO: 18, ~~SeqID#19~~ SEQ ID NO: 19, ~~SeqID#20~~ SEQ ID NO: 20, and ~~SeqID#21~~ SEQ ID NO: 21 have been contemplated by the inventors. The encoded GHRH is a biologically active polypeptide; and the encoded functional biological equivalent of GHRH is a polypeptide that has been engineered to contain a distinct amino acid sequence while simultaneously having similar or improved biologically activity when compared to the GHRH polypeptide. One result of

expressing the encoded GHRH or functional biological equivalent thereof in a subject is the facilitation of growth hormone ("GH") secretion in the subject.

At Page 13:

[0021] Figure 3 shows the optimized nucleic acid sequence for the kanamycin gene (SEQ ID NO: 3) and the corresponding translated amino acid sequence (SEQ ID NO: 22);

[0023] Figure 5 shows the optimized nucleic acid sequence for the mGHRH gene (SEQ ID NO: 5) and the corresponding translated amino acid sequence (SEQ ID NO: 23);

[0024] Figure 6 shows the optimized nucleic acid sequence for the original mGHRH gene ("GHRH-m-ori") (SEQ ID NO: 24), and the optimized mGHRH gene ("GHRH-m-opt") (SEQ ID NO: 5) after removing some CpG islands and other motifs that can decrease protein expression, the changes did not effect the amino acid sequence;

[0025] Figure 7 shows a comparison of the translated amino acid sequence from the original ("GHRH-m-Ori") (SEQ ID NO: 25) and optimized nucleic acid sequence for the mouse GHRH gene ("GHRH-m-Opti") (SEQ ID NO: 23);

[0027] Figure 9 shows the optimized nucleic acid sequence for the rGHRH gene (SEQ ID NO: 6) and the corresponding translated amino acid sequence (SEQ ID NO: 26);

[0028] Figure 10 shows the optimized nucleic acid sequence for the original rGHRH gene ("GHRH-R-ori") (SEQ ID NO: 27), and the optimized rGHRH gene ("GHRH-R-opt") (SEQ ID NO: 6) after removing some CpG islands and other motifs that can decrease protein expression, the changes did not effect the amino acid sequence;

[0029] Figure 11 shows a comparison of the translated amino acid sequence from the original ("GHRH-R-Ori") (SEQ ID NO: 28) and optimized nucleic acid sequence for the rat GHRH gene ("GHRH-R-Opti") (SEQ ID NO: 26);

[0031] Figure 13 shows the optimized nucleic acid sequence for the bGHRH gene (SEQ ID NO: 7) and the corresponding translated amino acid sequence (SEQ ID NO: 29);

[0032] Figure 14 shows the optimized nucleic acid sequence for the original bGHRH gene ("GHRH-B-ori") (SEQ ID NO: 30), and the optimized bGHRH gene ("GHRH-B-opt") (SEQ ID NO: 7) after removing some CpG islands and other motifs that can decrease protein expression, the changes did not effect the amino acid sequence;

[0033] Figure 15 shows a comparison of the translated amino acid sequence from the original ("GHRH-B-Ori") (SEQ ID NO: 31) and optimized nucleic acid sequence for the bovine GHRH gene ("GHRH-B-Opti") (SEQ ID NO: 29);

[0035] Figure 17 shows the optimized nucleic acid sequence for the oGHRH gene (SEQ ID NO: 8) and the corresponding translated amino acid sequence (SEQ ID NO: 32);

[0036] Figure 18 shows the optimized nucleic acid sequence for the original oGHRH gene ("GHRH-O-ori") (SEQ ID NO: 33), and the optimized oGHRH gene ("GHRH-O-opt") (SEQ ID NO: 8) after removing some CpG islands and other motifs that can decrease protein expression, the changes did not effect the amino acid sequence;

[0037] Figure 19 shows a comparison of the translated amino acid sequence from the original ("GHRH-O-Ori") (SEQ ID NO: 34) and optimized nucleic acid sequence for the ovine GHRH gene ("GHRH-O-Opti") (SEQ ID NO: 32);

[0039] Figure 21 shows the optimized nucleic acid sequence for the cGHRH gene (SEQ ID NO: 35) and the corresponding translated amino acid sequence (SEQ ID NO: 36);

[0040] Figure 22 shows the optimized nucleic acid sequence for the original cGHRH gene ("GHRH-Chi-ori") (SEQ ID NO: 37), and the optimized cGHRH gene ("GHRH-Chi-opt") (SEQ ID NO: 35) after removing some CpG islands and other motifs that can decrease protein expression, the changes did not effect the amino acid sequence;

[0041] Figure 23 shows a comparison of the translated amino acid sequence from the original ("GHRH-Chi-Ori") (SEQ ID NO: 38) and optimized nucleic acid sequence for the chicken GHRH gene ("GHRH-Chi-Opti") (SEQ ID NO: 36) [[;]].

At Page 26:

[0084] **Optimized Plasmid Backbone**. One aspect of the current invention is the optimized plasmid backbone. The new synthetic plasmids presented below contain eukaryotic sequences that are synthetically optimized for species specific mammalian transcription. An existing pSP-HV-GHRH plasmid ("pAV0125") (~~SeqID#1~~ SEQ ID NO: 1), as shown in Figure 1 was synthetically optimized to form a new plasmid ("pAV0201")(~~SeqID#2~~ SEQ ID NO: 2). The plasmid pAV0125 was described in U.S. Patent 6,551,996 that was issued on April 23, 2003 titled "Super Active Porcine Growth Hormone Releasing Hormone Analog" with Schwartz, et al., listed as inventors, ("the Schwartz '996 Patent"). This 3,534 bp plasmid pAV0125 (~~SeqID #1~~ SEQ ID NO: 1) contains a plasmid backbone with various component from different commercially available plasmids, for example, a synthetic promoter SPc5-12 (~~SeqID #15~~ SEQ ID NO: 15), a modified porcine GHRH sequence (~~SeqID #4~~ SEQ ID NO: 4), and a 3'end of human growth hormone (~~SeqID #10~~ SEQ ID NO: 10). The new optimized synthetic expression vector (~~SeqID #2~~ SEQ ID NO: 2) contains 2,739 bp and is shown in Figure 2. The therapeutic encoded gene for the optimized plasmid in Figure 2 may also include optimized nucleic acid sequences that encode the following modified GHRH molecules.

ENCODED GHRH AMINO ACID SEQUENCE

wt-GHRH YADAIFTNSYRKVLGQLSARKLLQDIMSRQQGERNQEQGA-OH (SEQ ID NO: 39)

HV-GHRH HVDAIFTNSYRKVLAQLSARKLLQDILNRQQGERNQEQGA-OH (SEQ ID NO: 40)

TI-GHRH YIDAIFTNSYRKVLAQLSARKLLQDILNRQQGERNQEQGA-OH (SEQ ID NO: 41)

TV-GHRH YVDAIFTNSYRKVLAQLSARKLLQDILNRQQGERNQEQGA-OH (SEQ ID NO: 42)

15/27/28-**GHRH** YADAIFTNSYRKVLAQLSARKLLQDILNRQQGERNQEQGA-OH (SEQ ID NO: 43)

At Page 27:

[0086] An example of this new optimized synthetic expression vector was denoted as pAV0201 (~~SeqID#2~~ SEQ ID NO: 2). In order to construct pAV0201 (~~SeqID#2~~ SEQ ID NO: 2), the unwanted sequences from the pAV0125 (~~SeqID#1~~ SEQ ID NO: 1) were initially removed. A software program called Vector NTI (version 7.0) was used to generate and match sequences that could be compared and were known to be extraneous (e.g. LacZ promoter). There are many programs such as Vector NTI (version 7.0) that are known in the art and could have been used

with similar results to compare and identify specific nucleic acid sequences. Once the extraneous DNA sequences were identified in the pAV0125 plasmid, they were removed by from the plasmid creating a truncated-pAV0125 plasmid. The Gene Forge® optimized synthetic sequences were used to produced codon frequencies that were matched in target and host organisms to ensure proper folding. Gene Forge® was also used to identify and correct a number of deleterious structural elements in the relevant nucleic acid sequences. For example, a bias of GC content can be used to increase mRNA stability or reduce secondary structures; tandem repeat codons or base runs that may impair the gene can be minimized with codon optimization; modification of ribosome binding sites and mRNA degradation sites can be utilized; codon optimization can also reduce or eliminate problem secondary structures within the transcribed mRNA. Although Gene Forge® is a proprietary product of Aptagen that speeds codon optimization analysis, publicly available databases are available that allow a person with average skill in the art to replicate codon optimization protocol.

At Page 28:

[0087] The pAV0125 plasmid contained a human Growth Hormone poly adenylation region that was approximately 618 bp. The original 618 bp region contained multiple poly adenylation sites and was reduced to only one. As a result over 400 bp were removed to an optimized length of 190bp (~~SeqID #10~~ SEQ ID NO: 10). Another 210bp poly A site is ~~SeqID #16~~ SEQ ID NO: 16. The origin of replication (~~SeqID #12~~ SEQ ID NO: 12) was not altered.

At Page 29:

[0089] As a result of the above modifications to the plasmid backbone, a new synthetic plasmid as shown in Figure 2 was constructed. The pAV0201 optimized plasmid comprises a 2,739 bp circular plasmid (~~SeqID#2~~ SEQ ID NO: 2). The pAV0201 plasmid contains at least one eukaryotic coding region, and at least one prokaryotic coding sequence, wherein it has been contemplated that the eukaryotic coding region contains a modified growth hormone releasing hormone ("GHRH"). The pAV0201 plasmid also contains a poly A signal, wherein the human growth hormone poly A has been utilized. The pAV0201 plasmid also contains a eukaryotic promoter, and it has been contemplated that the c5-12 synthetic eukaryotic promoter of skeletal actin will be used, although other may be equally useful. The pAV0201 also

contains a prokaryotic promoter. The prokaryotic promoter is PNEO, and a 19-47 bp sequence of transposon fragment ("Tn5") with accession number V00618. Additionally one NEO ribosome binding site ("RBS") is present in the pAV0201 plasmid. A complementary origin of replication sequence ("pUC ori") from the pUC18 plasmid (e.g. 685-1466 bp of pUC18). A 5' untranslated region ("5' UTR") was inserted into the pAV0201 plasmid. The 5' UTR is from human growth hormone hGH 5' UTR (i.e. 504-557 bp) accession number M13438.

At Page 30:

[0091] One aspect of the current invention is the insertion of the codon optimized nucleic acid expression sequence for mouse GHRH ("mGHRH") (~~SeqID#5~~ SEQ ID NO: 5) into the pAV0201 plasmid backbone to give pAV0202 (~~SeqID#17~~ SEQ ID NO: 17). A schematic representation of the optimized nucleic acid expression sequence for mGHRH is shown in Figure 4. The optimized 228bp mGHRH fragment was sub-cloned into the pAV0201 vector using the Nco I and Hind III restriction enzyme cut sites, and standard methods known to one with ordinary skill in the art of molecular biology. Figure 5 shows a detailed nucleic acid and amino acid sequence of the mGHRH motif, wherein all changes to the nucleic acid expression sequences are labeled in bold. The nucleic acid alignment between the original sequence (GHRH-M Ori) and Gene Forge optimized sequence (GHRH-M Opti) are shown in Figure 6, changes are labeled in bold. Figure 7 shows a comparison to indicate that the amino acid sequence has not changed due to codon optimization.

At Page 31:

[0092] Another aspect of the current invention is the insertion of the codon optimized nucleic acid expression sequence for rat GHRH ("rGHRH") (~~SeqID#6~~ SEQ ID NO: 6) into the pAV0201 plasmid backbone to give pAV0203 (~~SeqID#18~~ SEQ ID NO: 18). A schematic representation of the optimized nucleic acid expression sequence for rGHRH is shown in Figure 8. The optimized 231bp rGHRH fragment was sub-cloned into the pAV0201 vector using the Nco I and Hind III restriction enzyme cut sites, and standard methods known to one with ordinary skill in the art of molecular biology. Figure 9 shows a detailed nucleic acid and amino acid sequence of the rGHRH motif, wherein all changes to the nucleic acid expression sequences are labeled in bold. The nucleic acid alignment between the original sequence (GHRH-R Ori)

and Gene Forge optimized sequence (GHRH-R Opti) are shown in Figure 10, changes are labeled in bold. Figure 11 shows a comparison to indicate that the amino acid sequence has not changed due to codon optimization.

[0093] Another aspect of the current invention is the insertion of the codon optimized nucleic acid expression sequence for bovine GHRH ("bGHRH") (~~SeqID#7~~ SEQ ID NO: 7) into the pAV0201 plasmid backbone to give pAV0204 (~~SeqID#19~~ SEQ ID NO: 19). A schematic representation of the optimized nucleic acid expression sequence for bGHRH is shown in Figure 12. The optimized 222bp bGHRH fragment was sub-cloned into the pAV0201 vector using the Nco I and Hind III restriction enzyme cut sites, and standard methods known to one with ordinary skill in the art of molecular biology. Figure 13 shows a detailed nucleic acid and amino acid sequence of the bGHRH motif, wherein all changes to the nucleic acid expression sequences are labeled in bold. The nucleic acid alignment between the original sequence (GHRH-B Ori) and Gene Forge optimized sequence (GHRH-B Opti) are shown in Figure 14, changes are labeled in bold. Figure 15 shows a comparison to indicate that the amino acid sequence has not changed due to codon optimization.

At Page 32:

[0094] Another aspect of the current invention is the insertion of the codon optimized nucleic acid expression sequence for ovine GHRH ("oGHRH") (~~SeqID#8~~ SEQ ID NO: 8) into the pAV0201 plasmid backbone to give pAV0205 (~~SeqID#20~~ SEQ ID NO: 20). A schematic representation of the optimized nucleic acid expression sequence for oGHRH is shown in Figure 16. The optimized 222bp oGHRH fragment was sub-cloned into the pAV0201 vector using the NcoI and Hind III restriction enzyme cut sites, and standard methods known to one with ordinary skill in the art of molecular biology. Figure 17 shows a detailed nucleic acid and amino acid sequence of the oGHRH motif, wherein all changes to the nucleic acid expression sequences are labeled in bold. The nucleic acid alignment between the original sequence (GHRH-O Ori) and Gene Forge optimized sequence (GHRH-O Opti) are shown in Figure 18, changes are labeled in bold. Figure 19 shows a comparison to indicate that the amino acid sequence has not changed due to codon optimization.

[0095] Another aspect of the current invention is the insertion of the codon optimized nucleic acid expression sequence for chicken GHRH ("cGHRH") (~~SeqID#9~~ SEQ ID NO: 9) into the pAV0201 plasmid backbone to give pAV0206 (~~SeqID#21~~ SEQ ID NO: 21). A schematic representation of the optimized nucleic acid expression sequence for cGHRH is shown in Figure 20. The optimized 234bp cGHRH fragment was sub-cloned into the pAV0201 vector using the Nco I and Hind III restriction enzyme cut sites, and standard methods known to one with ordinary skill in the art of molecular biology. Figure 21 shows a detailed nucleic acid and amino acid sequence of the cGHRH motif, wherein all changes to the nucleic acid expression sequences are labeled in bold. The nucleic acid alignment between the original sequence (GHRH-C Ori) and Gene Forge optimized sequence (GHRH-C Opti) are shown in Figure 22, changes are labeled in bold. Figure 23 shows a comparison to indicate that the amino acid sequence has not changed due to codon optimization. For this particular sequence, the chicken pre-pro hormone signal was replaced with the more compact, shorter rat pre-pro sequence.